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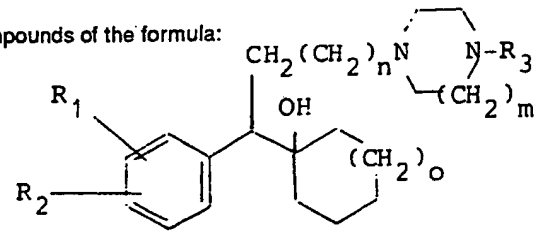
C2C CAA C1175 C1600 C1620 C1626 C215 C22Y C220 C221 C225 C226 C246 C25Y C250 C252 C28X C30Y C31Y C311 C313 C338 C339 C36Y C360 C363 C50Y C509 C623 C624 C662 C694 C697 C699 C80Y C802 U1S S2417

(56) Documents cited
US 2971955 A

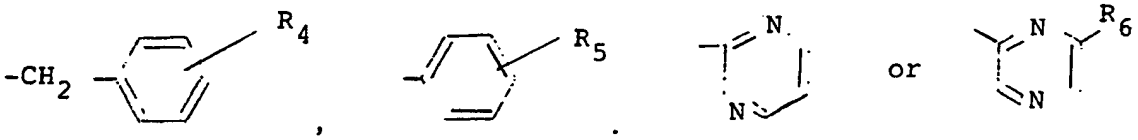
(58) Field of search
UK CL (Edition J) C2C CWH
CAS Online

(54) Substituted cycloalkanols

(57) Compounds of the formula:



in which m is one of the integers 1, 2 or 3; n is one of the integers 0, 1 or 2; o is one of the integers 0, 1 or 2; R_1 and R_2 are, independently, hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, trifluoromethyl, halo, or, when taken together, 3, 4–methylenedioxy; R_3 is alkyl,



where R_4 and R_5 are, independently, hydrogen, hydroxy; 1, alkyl, alkoxy, alkanoyloxy, halo or trifluoromethyl; and R_6 is hydrogen or halo; or a pharmaceutically acceptable salt thereof, are useful in treatment of psychiatric disorders.

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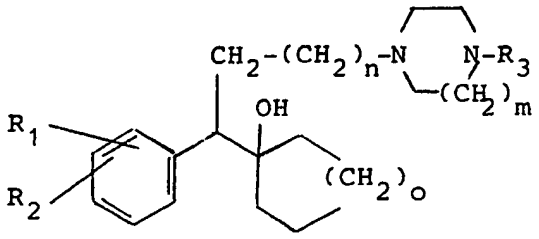
SUBSTITUTED CYCLOALKANOLS

In accordance with this invention there is provided a group of substituted cycloalkanols which are useful in the treatment of psychiatric disorders classified as psychosis, depression and anxiety. The compounds of this invention have the general formula:



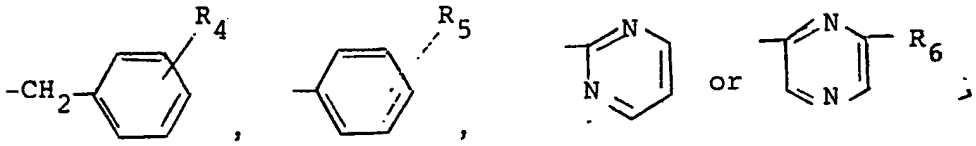
(I)

in which

m is one of the integers 1, 2 or 3;
n is one of the integers 0, 1 or 2;
o is one of the integers 0, 1 or 2;

R_1 and R_2 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, trifluoromethyl, halo, or when taken together, 3,4-methylenedioxy;

R_3 is alkyl of 1 to 3 carbon atoms,

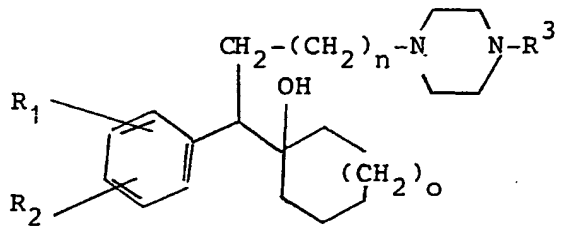


where R_4 and R_5 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, halo or trifluoromethyl; and

R_6 is hydrogen or halo.

or a pharmaceutically acceptable salt thereof.

Within this group of compounds there resides a preferred group of compounds which in addition to their antidepressant activity, also possess anti-anxiety properties. The most preferred antidepressant-anti-anxiety compounds of this invention present the structural formula:



(Ia)

in which

n is one of the integers 0, 1 or 2;

o is one of the integers 0, 1 or 2;

R_1 is hydrogen, alkoxy of 1 to 3 carbon atoms or hydroxy;

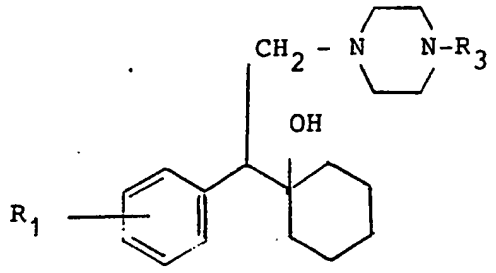
R_2 is alkoxy of 1 to 3 carbon atoms or hydroxy and, when R_1 is hydrogen and n is zero, R_2 can be halo or trifluoromethyl; or

R_1 and R_2 taken together are 3,4-methylenedioxy; and

R_3 is benzyl, chlorobenzyl, trifluoromethylbenzyl, alkoxybenzyl, chlorophenyl, trifluoromethylphenyl or alkoxyphenyl in which said alkoxy groups contain from 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

In addition, there resides within the group of compounds of this invention some purely antidepressant compounds of the formula:



(Ib)

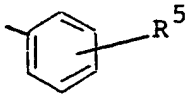
in which

R_1 is halo, trifluoromethyl, hydroxy or alkoxy of 1 to 6 carbon atoms; and R_3 is alkyl of 1 to 3 carbon atoms, preferably methyl.

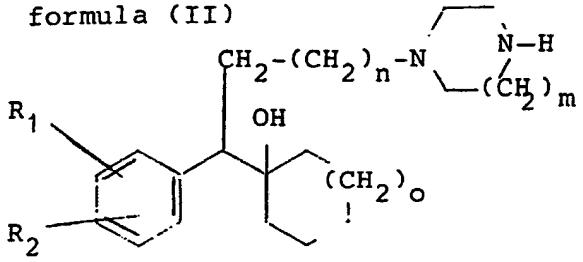
or a pharmaceutically acceptable salt thereof.

Substitution of the benzene ring, in all of these compounds, is preferably by hydroxy, methoxy, halo and trifluoromethyl groups. The halo groups include chloro, bromo, iodo and fluoro substituents. The pharmaceutically acceptable salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic and similar acids. For parenteral administration, the use of water soluble salts is preferred, while either the free base or the pharmaceutically acceptable salts are applicable for oral administration.

The compounds of the invention may be prepared by conventional methods. For example, the compounds of the invention in which R^3 is other than

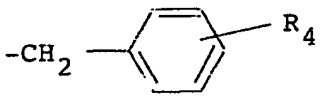


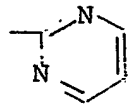
may be prepared by alkylation of an intermediate of formula (II)



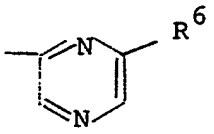
(II)

in which
m, n, o, R_1 and R_2 have the meanings given above). By "alkylation" is meant introducing on to the nitrogen atom of the heterocyclic ring a R_3, radical (where R_3, is





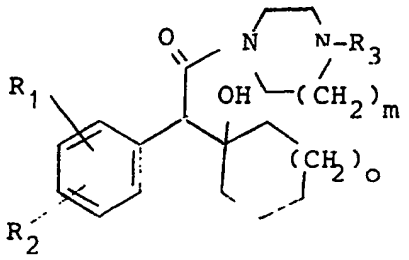
or



where R_4 and R_6 have the meanings given above. In one method of carrying out the alkylation, the intermediate of formula II is reacted with an alkylating agent, such as a compound of formula R_3X [where R_3 is as defined above and X is a leaving group such as an organosulphonylony group (eg mesyl or tosyl) or halo, preferably chloro]. The reaction may be carried out under conventional conditions eg in the

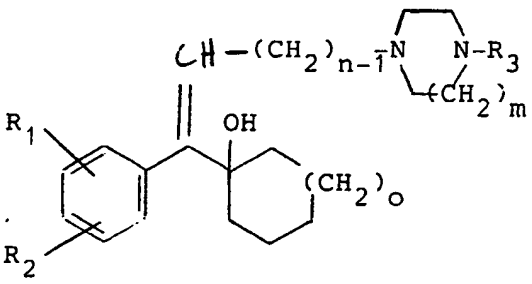
presence of an acid acceptor such as an alkali metal carbonate or triethylamine.

The compounds of the invention may also be prepared by reduction of a compound of formula



(III)

or



(IV)

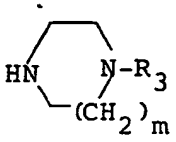
(where m, n, o, R_1, R_2 and R_3 have the meanings given above).

The amides of formula III may be reduced with, for example, a hydride reducing agent eg. borane in tetrahydrofuran. The reduction of the amide (III) gives a compound of the invention in which n is zero.

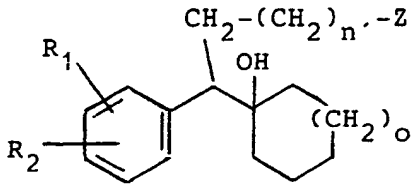
Reduction of the unsaturated compounds of formula IV gives compounds of the invention in which n is 1 or 2. The reduction may be carried out by, for example,

catalytic hydrogenation. When R_3 is benzyl or substituted benzyl this group is removed by catalytic hydrogenation to give an intermediate of formula II and the desired R_3 group is reintroduced by the method given above.

Another method of preparing the compounds of the invention in which n is 1 or 2 comprises reacting a heterocyclic compound of formula



(where m and R_3 have the meanings given above) with a compound of formula



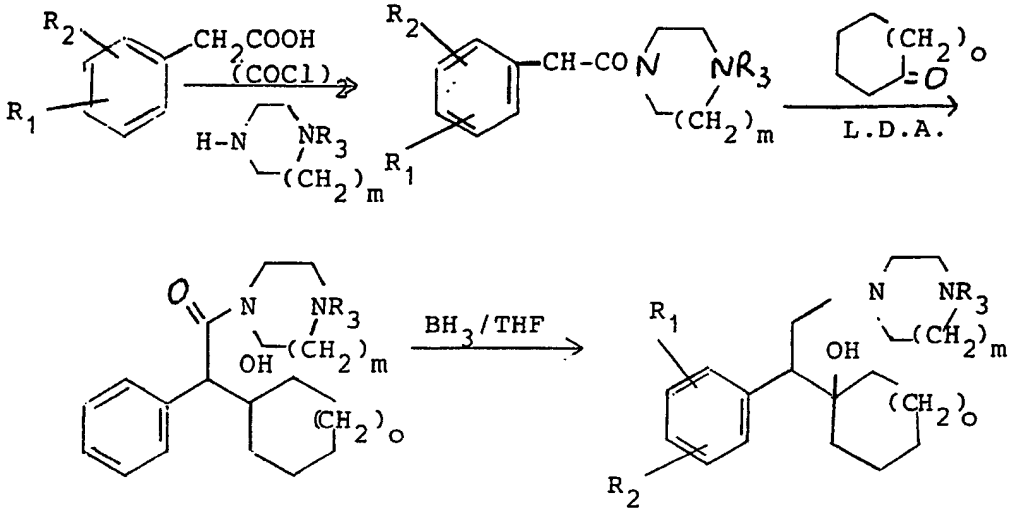
(V)

(where o, R_1 and R_2 have the meanings given above, n' is 1 or 2 and Z is a leaving group such as an organosulphonyloxy group or halo).

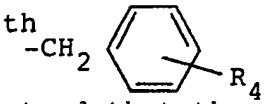
The compounds of formula (II), (III), (IV) and (V) may be prepared by methods known in the art. For example the compounds of formula (II) can be prepared by catalytic hydrogen of the compounds of the invention in which R_3 is benzyl. This process and other methods for preparing compounds of formulae (II), (III) and (IV) are shown, by way of example in the following detailed procedures illustrating the preparation of compounds of the invention. Compounds of formula (V) may be prepared from the corresponding alcohols which in turn

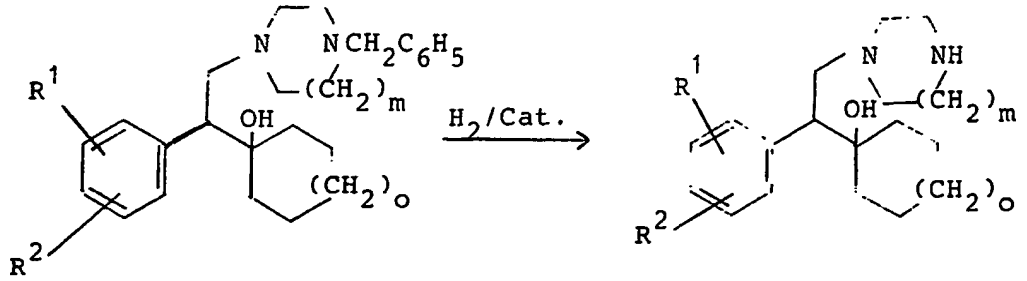
may be prepared by processes known in the art.

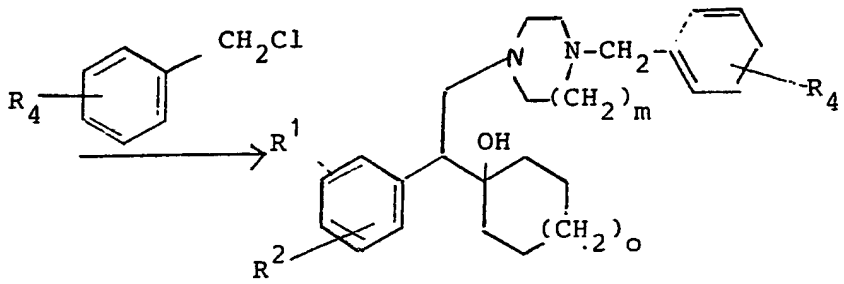
In general, the compounds in which n is equal to zero may be efficiently obtained by the following procedure:



The amide produced from the appropriately substituted phenylacetic acid is treated with a cycloalkanone and a hydroxycycloalkyl intermediate is obtained. This is converted to the desired end product using a borane/THF reduction following the procedure of Brown et al.,J Org.Chem., 38, 912 (1973). When R_3 is $-CH_2-C_6H_5$, it may be removed by catalytic or transfer hydrogenation and a different R_3 group may be reintroduced, tailored as desired.

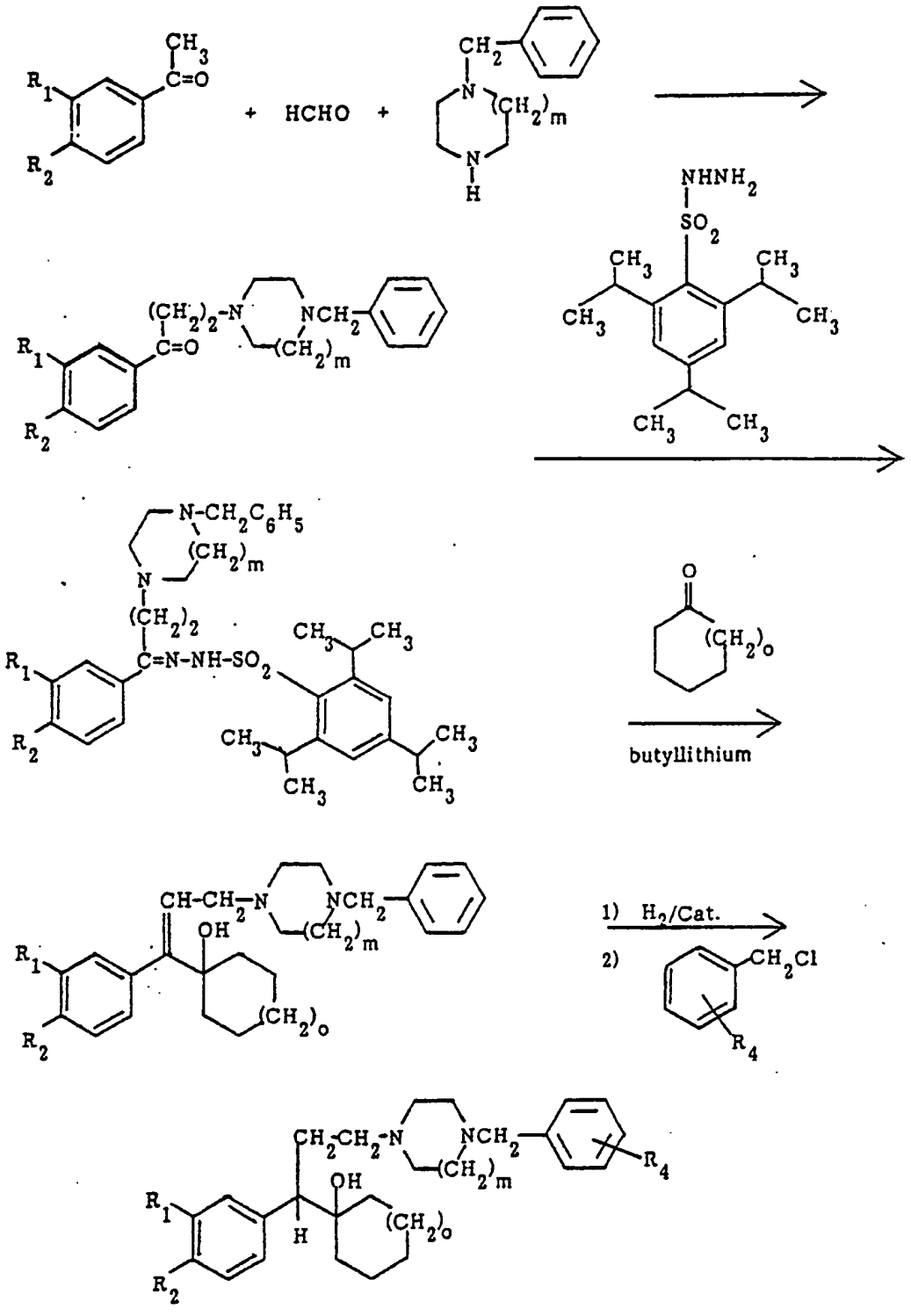
The following procedure illustrates the tailoring of the R_3 substituent with  but it is to be understood that the other variables representing R_3 in the group of compounds of this invention are similarly applicable and their preparation is illustrated in the working examples:



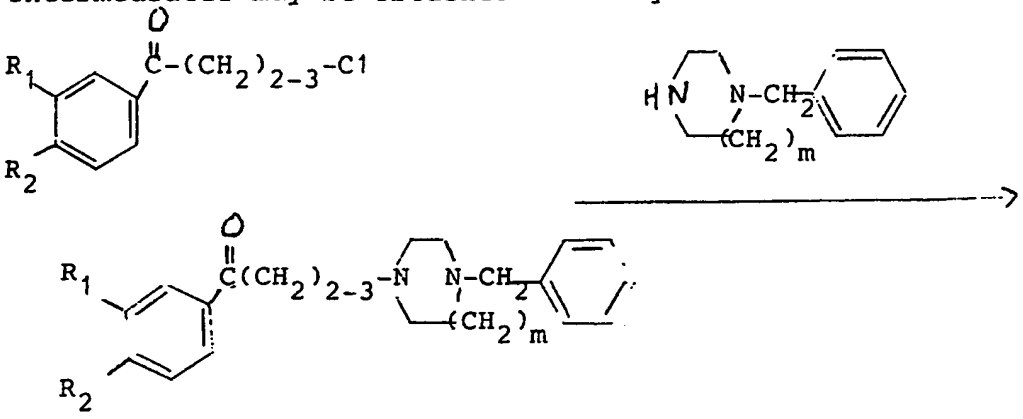


In the removal of an N-benzyl group by catalytic or transfer hydrogenation, R_1 and R_2 cannot be a halogen because hydrogenolysis of aromatic halogen occurs during removal of the benzyl substituent.

When n is one or two, a different preparative technique may be employed as depicted by the following representative steps in which n has the value of one:

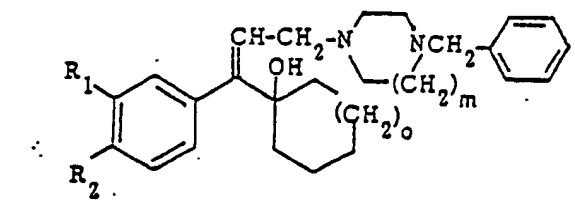

+ HCHO +
butyllithium
1) H2/Cat.
2)

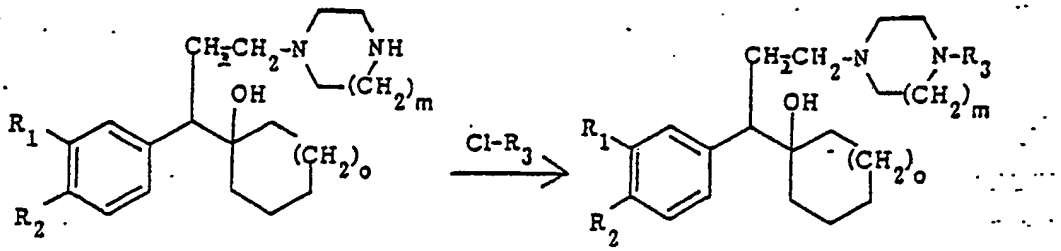
In this procedure, the propiophenone and butyrophenone intermediates may be obtained directly as follows:



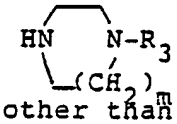
Use of the butyrophenone intermediate gives by analogy, a compound of the invention in which n is two.

The propiophenone or butyrophenone intermediates obtained from either process, may be converted to the tris-(1-methylethyl)benzenesulfonylhydrazone using the Bond modification of the Shapiro reaction [Chamberlain et al., J.Org.Chem., 43, 147 (1978)]. The hydrazone yields a vinyl anion which condenses with a cycloalkanone to form the cycloalkanol. Catalytic hydrogenation debenzylates the piperazine moiety and gives a mixture of the saturated and unsaturated intermediate products. Catalytic transfer hydrogenation using, eg sodium formate/formic acid as hydrogen donor, yields saturated debenzylated intermediates. The desired, saturated end products of the reaction sequence may be obtained by reintroduction of the R_3 group as follows:





In this procedure, the R_1 and R_2 substituents are present as methoxy substituents in the 3-and/or 4-positions of the benzene ring for optimum product yields. If a starting material of formula



in which R_3 is other than optionally substituted benzyl, is used catalytic dehydrogenation does not remove the R_3 group and hence a compound of the invention is directly obtained without reintroducing the R_3 group.

During the course of the synthesis of the end compounds of the invention by means of processes identified above, any hydroxy group may be in the free form or in the form of hydroxy protected by a removable protecting group. The protected form is recommended where the hydroxy group may otherwise undergo an undesired reaction. Examples of protecting groups for the hydroxy substituent are given in Protective Groups in Organic Chemistry edited by J.F.W. McOmie, Chapters 3 and 4 (pages 95-182) published by Plenum Press (1973), and Protective Groups in Organic Chemistry by T.W. Greene, Chapters 2 and 3 (pages 10 to 113) published by

John Wiley and Sons (1981). The protecting group may be removed at a suitable later stage in the synthesis.

The final products contain an asymmetric center which, via conventional techniques of resolution, affords the individual optical isomers of the compounds.

In the production of the compounds of this invention, the preparation of certain key intermediates are best illustrated by the following detailed preparative schemes:

I

n=1

1-[1-(3-Methoxyphenyl)-3-(piperazinyl)propyl]-cyclohexanol

a) 1-(3-Methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propanone

A mixture of 3-methoxyacetophenone (53.8 g, 0.35 mole), paraformaldehyde (12.6 g), 1-benzylpiperazine dihydrochloride (106.2 g, 0.43 mole), ethanol (560 mL) and concentrated HCl (1.05 mL) was stirred and refluxed for 16 hours. The reaction mixture was cooled in ice and the product separated. The dihydrochloride was filtered using ice-cold ethanol, washed with diethyl ether and dried in a desiccator under vacuum. Yield 50.8 g, m.p. 256-259°°C.

Elemental Analysis for: $C_{21}H_{26}N_2O_2 \cdot 2HCl$

Calculated	C,61.31;H, 6.86;N, 6.81
Found	C,61.25;H, 6.99;N, 6.89

b) 2,4,6-Tris-(1-methylethyl)benzenesulfonic acid [1-(3-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]propylidene]hydrazide

To a suspension of 2,4,6-tris-(1-methylethyl) benzenesulfonylhydrazide (30 g, 0.01 mole) in a mixture of methanol (80 mL), diethyl ether (70 mL) and 5N isopropanolic HCl (30 mL) was added 1-(3-methoxyphenyl)-3-[4-(phenylmethyl)-1-propanone, dihydrochloride (42 g, 0.1 mole) and water (45 mL). The mixture was stirred at room temperature for 16 hours. The solid precipitate was filtered, washed with ethyl acetate and air dried. The free base was obtained as follows: the solid was partitioned between ethyl acetate and 4N NaOH solution (800 mL, 1:1 (v/v)). The phases were separated. The aqueous phase was extracted with ethyl acetate and the combined organic phase washed with brine, dried over magnesium sulfate and evaporated. The title compound, as a solid residue, was triturated with hexane and air dried, yield 42 g, m.p. 256-259°C.

Elemental Analysis for: $C_{36}H_{50}N_4O_3S \cdot 1/3\ H_2O$

Calculated:	C, 69.20; H, 8.12; N, 8.97
Found:	C, 69.30; H, 7.98; N, 8.85

c) 1-[1-(3-Methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propenyl]cyclohexanol

2,4,6-Tris(1-methylethyl)benzenesulfonic acid [1-(3-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]propylidene]hydrazide (42 g, 0.068 mole) was dissolved in dry dimethoxyethane (575 mL) under nitrogen with stirring. The solution was cooled to -78°C. and n-butyllithium (78 mL, 2.5 M) was added dropwise. The mixture was allowed to warm to 0°C. and was stirred at this temperature for 15 minutes, during which time the reaction mixture became dark brown in color. The mixture was cooled to -50°C. and excess cyclohexanone (11.5 mL) added. The reaction mixture was stirred for 1.5 hours during which time the color dissipated as the reaction approached ambient temperature. The mixture was poured into a diethyl ether-N HCl mixture (400 mL, 1:1 v/v). The phases were separated. The aqueous phase was extracted with diethyl ether and the organic phase with N HCl. The combined aqueous (acidic) phase was basified with solid KOH and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium

sulfate and evaporated to an amorphous solid. Wt. 14 g. The product was dissolved in diethyl ether and the solution treated with excess 4N-isopropanolic HCl. The dihydrochloride of the title compound was obtained, m.p. 230-232°C.

Elemental Analysis for: $C_{27}H_{36}N_2O_2 \cdot 2HCl \cdot H_2O$

Calculated: C, 63.39; H, 7.88; N, 5.48

Found: C, 63.35; H, 7.78; N, 5.81

d) 1-[1-(3-Methoxyphenyl)-3-(1-piperazinyl)propyl]cyclohexanol

A solution of 1-[1-(3-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propenyl]cyclohexanol (3.09 g, 7.1 mmole) in ethanol (50 mL) containing sodium formate (0.5 g, 7.1 mmole) and formic acid (1.5 g, 30 mmole) was added to a suspension of 10% Pd/C (3.0 g) in ethanol (50 mL) and the mixture refluxed for 2 hours under nitrogen. The catalyst was filtered and the filtrate evaporated. The residue was partitioned between 4N sodium hydroxide (200 mL) and ethyl acetate (200 mL). The layers were separated. The aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated to obtain the title compound as an oil.

Yield 1.9 g. Mass spectral analysis: Molecular weight by chemical ionization M+1 at 334.

II

n=1

1-[1-(4-Methoxyphenyl)-3-(piperazinyl)propyl]cyclohexanol

a) 1-[1-(4-Methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propenyl]cyclohexanol

By replacing 2,4,6-tris(1-methylethyl)benzenesulfonic acid [1-(3-methoxyphenyl)-3-[4-phenylmethyl-1-piperazinyl]propylidene]hydrazide in I(c) with a molar equivalent amount of 2,4,6-tris(1-methylethyl)benzenesulfonic acid [1-(4-methoxyphenyl)-3-[4-phenylmethyl-1-piperazinyl]propylidene]hydrazide and following the procedure described therein, 1-[1-(4-

methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propenyl]cyclohexanol was obtained in 80% yield. The product was converted to the dihydrochloride using 4N-isopropanolic HCl, m.p. 214-216°C., yield 42%.

Elemental Analysis for: $C_{27}H_{30}N_2O_2 \cdot 2\ HCl$

Calculated: C, 65.71; H, 7.76; N, 5.68

Found: C, 65.41; H, 7.39; N, 5.79

b) 1-[1-(4-Methoxyphenyl)-3-(1-piperazinyl)propyl]cyclohexanol

A solution of 1-[1-(4-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propenyl]cyclohexanol, dihydrochloride (14.6 g, 29.6 mmole) in ethanol (250 mL) was hydrogenated in a Parr apparatus over 10% Pd/C for 65 hours. The catalyst was filtered and the filtrate evaporated. The residue was partitioned between ethyl acetate (120 mL) and N sodium hydroxide (65 mL). The layers were separated. The aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated to obtain the title compound as an oil. Wt. 7.8 g. Mass spectral analysis: Molecular weight by C.I.M.S.: M+1 334.

III

n=2

1-[1-(4-Methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]-1-butenyl]cyclohexanol

a) 1-(4-Methoxyphenyl)-4-[4-phenylmethyl)-1-piperazinyl]-1-butanone

A mixture of Y-chloro-p-methoxybutyrophenone (45 g, 210 mole) 1-benzylpiperazine (35 mL, 200 mole) and anhydrous potassium carbonate (250 g) in methylisobutylketone (800 mL) was refluxed under nitrogen for 40 hours. The reaction mixture was cooled, poured into a beaker containing ice, then ethyl acetate was added. The layers were separated. The organic phase was washed with water, brine, dried over K_2CO_3 and evaporated to an oil. This residue was dissolved in diethyl ether (200 mL) and treated with excess 4N-isopropanolic HCl. The hydrochloride was obtained. Wt. 53 g. The product was purified as free base using column chromatography. It was then converted to the dihydrochloride of the title compound, m.p. 173-175°C.

Elemental Analysis for: $C_{23}H_{28}N_2O_2$ 2 HCl 1 1/2 H_2O

Calculated: C, 58.4; H, 6.69; N, 6.19

Found: C, 58.48; H, 7.09; N, 6.05

b) 1-[1-(4-Methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]-1-butenyl]cyclohexanol

By replacing 2,4,6-tris-(1-methylethyl)benzenesulfonic acid [1-(3-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]propylidene]hydrazide in I(c) with 2,4,6-tris-(1-methylethyl)benzenesulfonic acid [1-(4-methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]butylidene]hydrazide and following the procedure described therein, the title compound was obtained. The product was dissolved in diethyl ether and treated with an isopropanolic solution of succinic acid (2 equivalents). The di-succinate was obtained in crystalline form, m.p. 146-148°C.

Elemental Analysis for: $C_{28}H_{38}N_2O_2 \cdot 2\ C_4H_6O_4$

Calculated: C, 64.46; H, 7.53; N, 4.17

Found: C, 64.11; H, 7.29; N, 4.30

IV

n=0

a) 1-[(3-Methoxyphenyl)acetyl]-4-(phenylmethyl)piperazine

3-Methoxyphenylacetic acid (100 g, 600 mmole) was dissolved in methylene chloride (600 mL) and treated with oxalyl chloride (60 mL) and DMF (1 mL) at room temperature. The mixture was stirred for four hours until gas evolution ceased. The solvent was evaporated and the residue dried under vacuum to remove excess oxalyl chloride. The oil obtained was dissolved in methylene chloride (400 mL). Half of this solution (200 mL, approx. 300 mmole) was cooled in ice and treated with a solution of 1-benzylpiperazine (60 mL, 350 mmole) and triethylamine (30 mL) in methylene chloride (100 mL) dropwise. The mixture was stirred at room temperature for 16 hours. Sodium bicarbonate solution was added and the mixture stirred for 15 minutes. The layers were separated. The organic phase was washed with water, brine, dried over K_2CO_3 and evaporated to an oil. Wt. 90 g. A small portion was characterized as the hydrochloride, m.p. 229-231°C.

Elemental Analysis for: $C_{20}H_{24}N_2O_2 \cdot HCl$

Calculated: C, 66.74; H, 7.02; N, 7.79

Found: C, 66.78; H, 6.91; N, 7.87

b) 1-(3-Chlorophenyl)-4-[(3-methoxyphenyl)acetyl]piperazine

By replacing 1-benzylpiperazine with a molar equivalent amount of 3-chlorophenylpiperazine in IV(a) and following the procedure described therein, the title compound was obtained as an oil. Mass spectral analysis: Molecular weight by C.I.M.S.: 344.5 (M+345, 347).

c) 1-[(3-Methoxyphenyl)acetyl]-4-[3-(trifluoromethyl)phenyl]piperazine

By replacing 1-benzylpiperazine with a molar equivalent of 3-trifluoromethylphenylpiperazine in IV(a) and following the procedure described therein, the title compound was obtained as a crystalline solid, m.p. 99-101°C.

Elemental Analysis for: $C_{20}H_{21}N_2O_2F_3$

Calculated: C, 63.48; H, 5.61; N, 7.04

Found: C, 63.40; H, 5.59; H, 7.47

d) 1-[(3-Chlorophenyl)acetyl]-4-(3-chlorophenyl)piperazine

By replacing 3-methoxyphenylacetic acid in IV(b) with a molar equivalent amount of 3-chlorophenylacetic acid, the title compound was obtained as an oil.

e) 1-[(4-Fluorophenyl)acetyl]-4-(phenylmethyl)piperazine

By replacing 3-methoxyphenylacetic acid with a molar equivalent of 4-fluorophenylacetic acid in IV(a), the title compound was obtained as a crystalline solid, m.p. 99-101°C.

Elemental Analysis for: $C_{19}H_{21}N_2OF$

Calculated: C, 73.04; H, 6.79; N, 9.06

Found: C, 72.83; H, 6.57; N, 9.06

f) 1-(Phenylmethyl)-4-[3-[(trifluoromethyl)phenyl]acetyl]piperazine

By replacing 3-methoxyphenylacetic acid in IV(a) with a molar equivalent amount of 3-trifluoromethylphenylacetic acid and following the procedure described therein, the title product was obtained as an oil.

g) 1-[(3-Chlorophenyl)acetyl]-4-methyl piperazine

By replacing 1-benzylpiperazine in IV(d) with a molar equivalent amount of N-methyl piperazine and following the procedure described therein, the title compound was obtained as an oil.

h) 1-[(4-Methoxyphenyl)acetyl]-4-methyl piperazine

By replacing 3-methoxyphenylacetic acid with 4-methoxyphenylacetic acid and 1-benzyl piperazine in IV(a) with a molar equivalent amount of N-methyl piperazine, the above intermediate was obtained as an oil.

i) 1-Methyl-4-[3-(trifluoromethyl)acetyl]piperazine

By replacing 4-methoxyphenylacetic acid in IV(h) with a molar equivalent amount of 3-trifluoromethylphenylacetic acid, the intermediate was obtained as an oil.

j) 1-[(3-Fluorophenyl)acetyl]-4-methyl piperazine

By replacing 4-methoxyphenylacetic acid in IV(h) with a molar equivalent amount of 3-fluorophenylacetic acid, the above intermediate was obtained as an oil.

The following examples illustrate, without limitation, the method employed in production of the products of this invention.

Example 1

1-[1-(3-Methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-propyl]cyclohexanol

Benzyl chloride (0.88 g, 6.8 mmole) was added to a solution of 1-[1-(3-methoxyphenyl)-3-(1-piperazinyl)propyl]cyclohexanol (1.8 g, 5.4 mmole) in DMF (50 mL) containing cesium carbonate (5.3 g, 1.6 mmole). The reaction mixture was stirred for one hour at room temperature. Triethylamine (0.23 mL) was added and the reaction mixture stirred for an additional 24 hours. The solvent was evaporated and the residue partitioned between water and chloroform (50:50 v/v). The aqueous solution was extracted with chloroform and the combined organic solution washed with brine, dried over magnesium

sulfate and evaporated to an oil. Wt. 2.8 g. Column chromatography on silica gel with chloroform yielded 900 mg of pure product. This was dissolved in diethyl ether and treated with isopropanolic HCl affording the dihydrochloride salt, m.p. 249-257°C.

Elemental Analysis for: $C_{27}H_{38}N_2O_2 \cdot 2\ HCl \cdot 3/4\ H_2O$

Calculated: C, 63.71; H, 8.07; N, 5.50

Found: C, 64.09; H, 8.03; N, 5.50

Example 2

1-[1-(3-Methoxyphenyl)-3-[4-(2-pyrimidinyl)-1-piperazinyl]-propyl]cyclohexanol

By replacing benzyl chloride in Example 1 with a molar equivalent amount of 2-chloropyrimidine, the title compound was obtained as a dihydrochloride, hemihydrate, m.p. 172-174°C.

Elemental Analysis for: $C_{24}H_{34}N_4O_2 \cdot 2\ HCl \cdot 1/2\ H_2O$

Calculated: C, 58.53; H, 7.57; N, 11.38

Found: C, 59.07; H, 7.74; N, 11.13

Example 3

1-[3-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]-1-(3-methoxyphenyl)-propyl]cyclohexanol

By replacing benzyl chloride in Example 1 with a molar equivalent amount of 2,6-dichloropyrazine, the title compound was obtained as the hydrochloride, hydrate, m.p. 133-135°C.

Elemental Analysis for: $C_{24}H_{33}N_4O_2Cl \cdot HCl \cdot H_2O$

Calculated: C, 57.71; H, 7.26; N, 11.22

Found: C, 58.22; H, 7.14; N, 10.74

Example 4

1-[3-[4-[(3-Chlorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)propyl]cyclohexanol

By replacing benzyl chloride in Example 1 with 3-chlorobenzyl chloride and following the procedure described there, the title compound was obtained as the dihydrochloride, monohydrate, m.p. 241-243°C.

Elemental Analysis for: $C_{27}H_{37}N_2O_2Cl \cdot 2\ HCl \cdot H_2O$

Calculated: C, 59.18; H, 7.17; N, 5.11

Found: C, 59.10; H, 7.69; N, 5.29

Example 5

1-[3-[4-[(4-Chlorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)-propyl]cyclohexanol

By replacing benzyl chloride in Example 1 with a molar equivalent amount of 4-chlorobenzyl chloride and following the procedure described therein, the title compound was obtained as the dihydrochloride, hydrate, m.p. 253-258°C.

Elemental Analysis for: $C_{27}H_{37}N_2O_2Cl \cdot 2\ HCl \cdot H_2O$

Calculated: C, 59.18; H, 7.17; N, 5.11

Found: C, 59.58; H, 7.55; N, 5.23

Example 6

1-[1-(3-Methoxyphenyl)-3-[4-[(2-methoxyphenyl)methyl]-1-piperazinyl]propyl]cyclohexanol

By replacing benzyl chloride in Example 1 with a molar equivalent amount of 2-methoxybenzyl chloride, the title compound was obtained as the dihydrochloride, hemihydrate, m.p. 226-228°C.

Elemental Analysis for: $C_{28}H_{40}N_2O_3 \cdot 2\ HCl \cdot 1/2\ H_2O$

Calculated: C, 62.91; H, 8.11; N, 5.24

Found: C, 63.23; H, 8.13; N, 5.30

Example 7

1-[3-[4-[(3-Fluorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)propyl]cyclohexanol

By replacing benzyl chloride in Example 1 with a molar equivalent amount of 3-fluorobenzyl chloride, the title compound was obtained. The free base was dissolved in diethyl ether and treated with an isopropanolic solution of succinic acid (2 equivalents) yielding the di-succinate, hemihydrate, m.p. 131-133°C.

Elemental Analysis for: $C_{27}H_{37}O_2N_2F \cdot 2(CH_2COOH)_2 \cdot 1/2\ H_2O$

Calculated: C, 61.30; H, 7.35; N, 4.08

Found: C, 61.41; H, 7.09; N, 4.02

Example 8

1-[1-(4-Methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]-propyl]cyclohexanol

Benzyl chloride (0.4 mL, 3.5 mmole) was added to a solution of 1-[1-(4-methoxyphenyl)-3-(1-piperazinyl)propyl]cyclohexanol (760 mg, 2.3 mmol) in DMF (25 mL) containing cesium carbonate (2.3 g, 7.1 mmole). The reaction mixture was stirred at room temperature for 2 hours. Triethylamine (0.9 mL, 6.4 mmol) was added and the reaction mixture stirred at room temperature an additional 20 hours. The solvent was evaporated. The residue was partitioned between water (150 mL) and methylene chloride (80 mL). The layers were separated. The aqueous phase was extracted twice with methylene chloride (80 mL) and the combined organic solution washed with water, brine, dried over magnesium sulfate and evaporated to an oil. Wt. 900 mg. This was dissolved in diethyl ether and treated with 2 equivalents of oxalic acid. The dioxalate, hemihydrate was isolated. Wt. 500 mg., m.p. 225-227°C. Yield = 36%.

Elemental Analysis for: $C_{27}H_{38}N_2O_2 \cdot 2\ C_2H_2O_4 \cdot 1/2\ H_2O$

Calculated: C, 60.87; H, 7.09; N, 4.58

Found: C, 61.24; H, 7.27; N, 4.29

Example 9

1-[3-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]-1-(4-methoxyphenyl)-propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent amount of 2,6-dichloropyrazine, the title compound was obtained as the oxalate, monohydrate, m.p. 204-207°C.

Elemental Analysis for: $C_{24}H_{33}N_4O_2Cl \cdot H_2O \cdot C_2H_2O_4$

Calculated: C, 56.46; H, 6.74; N, 10.13

Found: C, 56.59; H, 6.48; N, 9.57

Example 10

1-[1-(4-Methoxyphenyl)-3-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent amount of 3-methoxybenzyl chloride and following the procedures described therein, the title compound was obtained. The free base was dissolved in diethyl ether and treated with 4N isopropanolic HCl, yielding the dihydrochloride, hemihydrate, m.p. 198-202°C.

Elemental Analysis for: $C_{28}H_{40}N_2O_3 \cdot 2\ HCl \cdot 1/2\ H_2O$

Calculated: C, 62.91; H, 8.11; N, 5.24

Found: C, 63.01; H, 8.27; N, 5.25

Example 11

1-[1-(4-Methoxyphenyl)-3-[4-[[3-(trifluoromethyl)phenyl]methyl]-1-piperazinyl]propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent amount of 3-trifluoromethylbenzyl chloride and following the procedure described therein, the title compound was prepared as the dioxalate, monohydrate salt, m.p. 215-219°C.

Elemental Analysis for: $C_{28}H_{37}N_2O_2F_3 \cdot 2\ C_2H_2O_4 \cdot H_2O$

Calculated: C, 55.80; H, 6.29; N, 4.06

Found: C, 55.23; H, 6.02; N, 4.00

Example 12

1-[3-[4-[(3-Chlorophenyl)methyl]-1-piperazinyl]-1-(4-methoxyphenyl)propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent amount of 3-chlorobenzyl chloride and following the procedures described therein, the title compound was obtained as the dioxalate, hemihydrate, m.p. 223-225°C.

Elemental Analysis for: $C_{27}H_{37}N_2O_2Cl \cdot 2\ C_2H_2O_4 \cdot 1/2\ H_2O$

Calculated: C, 57.62; H, 6.55; N, 4.34

Found: C, 57.76; H, 6.38; N, 4.46

Example 13

1-[1-(4-Methoxyphenyl)-3-[4-(2-methoxyphenyl)methyl]-1-piperazinyl]propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent of 2-methoxybenzyl chloride, the title compound was obtained as the dioxalate, m.p. 216-218°C.

Elemental Analysis for:	$C_{28}H_{40}N_2O_3 \cdot 2\ C_2H_2O_4$
Calculated:	C, 60.74; H, 7.01; N, 4.43
Found:	C, 60.80; H, 7.47; N, 3.99

Example 14

1-[1-(4-Methoxyphenyl)-3-[4-[[4-(trifluoromethyl)phenyl]methyl]-1-piperazinyl]propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent amount of 4-trifluoromethylbenzyl bromide and following the procedures described therein, the title compound was obtained as the free base. The oil was dissolved in diethyl ether and treated with an isopropanolic solution of succinic acid (2 eqs.) and the di-succinate, hemihydrate was obtained, m.p. 148-152°C.

Elemental Analysis for:	$C_{28}H_{37}N_2O_2F_3 \cdot 2\ C_4H_6O_4 \cdot 1/2\ H_2O$
Calculated:	C, 58.76; H, 6.85; N, 3.81
Found:	C, 58.82; H, 6.69; N, 3.76

Example 15

1-[1-(3-Methoxyphenyl)-2-[4-(phenylmethyl)-1-piperazinyl]-ethyl]cyclohexanol

Lithium di-isopropylamide (L.D.A.) was prepared by dissolving di-isopropylamine (144 mL) in THF (200 mL) followed by the addition of 2.7 moles N-butyllithium (37 mL). The solution was cooled to -78°C., and a solution of 1-[(3-methoxyphenyl)acetyl]-4-(phenylmethyl)piperazine (32 g, 100 mmole) in THF (100 mL) added slowly. The reaction mixture was stirred at -78°C. for 30 minutes. Excess cyclohexanone (2 equivalents) was added and the mixture stirred at -78°C. for 30 minutes. The reaction mixture was poured into saturated ammonium chloride solution (200 mL). The layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic

extract washed with brine, dried over K_2CO_3 and evaporated to an oil. The oil was dissolved in THF (100 mL) and added to an ice-cold solution of borane/-THF complex (200 mL, 200 mmole). The mixture was refluxed for 2 hours and cooled again in an ice/acetone bath. 6N HCl (50 mL) was slowly added and the reaction mixture refluxed for 1 hour. The reaction mixture was cooled in ice/acetone and basified with solid KOH pellets. The layers were separated. The organic layer was washed with brine, dried over K_2CO_3 and evaporated to an oil, Wt. 24 g. The product was dissolved in diethyl ether and treated with 2 equivalents of 4N-isopropanolic HCl. The dihydrochloride was isolated, m.p. 233-235°C.

Elemental Analysis for: $C_{25}H_{36}N_2O_2 \cdot 2\ HCl$

Calculated: C, 64.86; H, 7.95; N, 5.82

Found: C, 64.22; H, 8.04; N, 6.27

Example 16

1-[2-[4-(Phenylmethyl)]-1-piperazinyl]-1-[3-(trifluoromethyl)-phenyl]ethyl]cyclohexanol

By replacing 1-[(3-methoxyphenyl)acetyl]-4-phenylmethyl]piperazine in Example 15 with a molar equivalent amount of 1-[(3-trifluoromethyl)-phenyl]acetyl]-4-(phenylmethyl)piperazine, the title compound was obtained as the dihydrochloride, monohydrate.

Elemental Analysis for: $C_{26}H_{33}N_2OF_3 \cdot 2\ HCl \cdot H_2O$

Calculated: C, 58.09; H, 6.76; N, 5.21

Found: C, 58.23; H, 6.26; N, 5.16

Example 17

1-[1-(4-Fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]-ethyl]cyclohexanol

By replacing 1-[(3-methoxyphenyl)acetyl]-4-phenylmethyl]piperazine in Example 15 with a molar equivalent amount of 1-[(4-fluorophenyl)-acetyl]-4-(phenylmethyl)piperazine, the title compound was obtained as the dihydrochloride salt, hemihydrate.

Elemental Analysis for: $C_{25}H_{33}N_2OF \cdot 2\ HCl \cdot 1/2\ H_2O$

Calculated: C, 62.75; H, 7.24; N, 5.86

Found: C, 63.10; H, 7.39; N, 5.70

Example 18

1-[2-[4-(3-Chlorophenyl)-1-piperazinyl]-1-(3-methoxyphenyl)-ethyl]cyclohexanol

By replacing 1-[(3-methoxyphenyl)acetyl]-4-(phenylmethyl)piperazine with a molar equivalent amount of 1-(3-chlorophenyl)-4-[(3-methoxyphenyl)acetyl]piperazine in Example 15, the title compound was obtained as a dihydrochloride, m.p. 178-180°C.

Elemental Analysis for: $C_{25}H_{33}N_2O_2Cl \cdot 2\ HCl$

Calculated: C, 59.82; H, 7.03; N, 5.60

Found: C, 60.62; H, 7.10; N, 6.17

Example 19

1-[1-(3-Chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol

Replacement of 1-[(3-methoxyphenyl)acetyl]-4-(phenylmethyl)-piperazine in Example 15 with a molar equivalent amount of 1-[(3-chlorophenyl)acetyl]-4-(3-chlorophenyl)piperazine afforded the title compound as a dihydrochloride salt, m.p. 191-193°C.

Elemental Analysis for: $C_{24}H_{30}N_2O \cdot 2HCl$

Calculated: C, 56.93; H, 5.97; N, 5.53

Found: C, 56.35; H, 6.23; N, 5.75

Example 20

1-[1-(3-Methoxyphenyl)-2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]cyclohexanol

By replacing 1-[(3-methoxyphenyl)acetyl]-4-(phenylmethyl)piperazine in Example 15 with a molar equivalent amount of 1-[(3-methoxyphenyl)-acetyl]-4-[3-(trifluoromethyl)phenyl]piperazine and following the procedure described therein, the title compound was obtained as a citrate, hemihydrate, m.p. 150-152°C.

Elemental Analysis for: $C_{26}H_{33}N_2O_2F_3 \cdot C_6H_8O_7 \cdot 1/2\ H_2O$

Calculated: C, 57.91; H, 6.39; N, 4.22

Found: C, 58.19; H, 6.33; N, 4.02

Example 21

1-[1-(3-Methoxyphenyl)-2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]cyclopentanol

By replacing cyclohexanone with a molar equivalent amount of cyclopentanone in Example 20, the title compound was obtained. The free base was converted to the maleate salt, m.p. 158-160°C.

Elemental Analysis for: $C_{25}H_{31}N_2O_2F_3 \cdot C_4H_4O_4$

Calculated: C, 61.69; H, 6.28; N, 4.96

Found: C, 61.37; H, 6.11; N, 5.02

Example 22

1-[2-[4-[(3-Chlorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)ethyl]cyclohexanol

To a suspension of 10% Pd/C (2.4 g) in ethanol (50 mL) was added a solution of 1-[1-(3-methoxyphenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl cyclohexanol (13.2 g, 32.2 mmole) in ethanol containing 4N isopropanolic HCl (18 mL). Ammonium formate (8.2 g, 129 mmole) was added and the mixture refluxed for 2 hours. The hot solution was filtered and the filtrate evaporated. The residue was partitioned between ethyl acetate and 4N sodium hydroxide (100:100 v/v). The layers were separated. The aqueous phase was extracted with ethyl acetate and the combined organic solution washed with brine, dried over Na_2SO_4 and evaporated yielding the secondary amine, 1-[1-(3-methoxyphenyl)-2-[1-piperazinyl]ethyl]cyclohexanol, 9.5 g. This secondary amine, 2.3 g, 7.2 mmole was dissolved in DMF (65 mL). Cesium carbonate (7.1 g, 21.8 mmole) and 3-chlorobenzyl chloride (1.5 g, 9 mmole) were added and the mixture stirred at room temperature for one hour. The reaction mixture was then treated with triethylamine (0.3 mL) and stirring continued for 24 hours. The solvent was evaporated and the residue partitioned between water and chloroform. The layers were separated. The aqueous solution was extracted with chloroform and the combined organic extract washed with brine, dried over Na_2SO_4 and evaporated (crude yield 4.7 g). Column chromatography on silica gel with chloroform yielded pure product (1.4 g). This was dissolved in diethyl ether and treated with an isopropanolic solution of fumaric acid. The fumarate, hemihydrate salt was isolated, m.p. 188-191°C.

Elemental Analysis for: $C_{26}H_{35}N_2O_2Cl \cdot 2C_4H_4O_4 \cdot 1/2\ H_2O$

Calculated: C, 59.69; H, 6.63; N, 4.09

Found: C, 60.03; H, 6.16; N, 4.04

Example 23

1-[2-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]-1-(3-methoxyphenyl)ethyl]cyclohexanol

By replacing 3-chlorobenzyl chloride with a molar equivalent amount of 2,6-dichloropyrazine in Example 22 and following the procedures described therein, the title compound was obtained. The free base was converted to the maleate salt, m.p. 157-158°C.

Elemental Analysis for: $C_{23}H_{31}N_4O_2Cl \cdot C_4H_4O_4$

Calculated: C, 59.28; H, 6.45; N, 10.24

Found: C, 59.29; H, 6.67; N, 10.22

Example 24

1-[1-(4-Methoxyphenyl)-3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]cyclohexanol

By replacing benzyl chloride in Example 8 with a molar equivalent amount of 2-chloropyrimidine and following the procedure described therein, the title compound was obtained as the free base. This was then converted to the oxalate salt, m.p. 193-196°C.

Elemental Analysis for: $C_{24}H_{34}N_4O_2 \cdot C_2H_2O_4$

Calculated: C, 62.38; H, 7.25; N, 11.19

Found: C, 62.04; H, 7.26; N, 10.75

Example 25

1-[1-(3-Fluorophenyl)-2-(4-methyl)-1-piperazinyl-ethyl]cyclohexanol

By replacing 1-[(3-methoxyphenyl)acetyl]-4-phenylmethylpiperazine in Example 15 with a molar equivalent amount of 1-[(3-fluorophenyl)-acetyl]-4-methyl piperazine, the title compound was obtained as a dihydrochloride, m.p. 264-266°C.

Elemental Analysis for: $C_{19}H_{29}N_2OF \cdot 2\ HCl$

Calculated: C, 58.01; H, 7.94; N, 7.12

Found: C, 57.79; H, 7.86, N, 6.96

Example 26

1-[1-(3-Chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol

By replacing 1-(3-methoxyphenyl)acetyl-4-phenylmethylpiperazine in Example 15 with a molar equivalent amount of 1-(3-chlorophenyl)acetyl-4-methyl piperazine, the title compound was obtained as a dihydrochloride, m.p. 253-255°C.

Elemental Analysis for: $C_{19}H_{29}N_2OCl \cdot 2HCl$

Calculated: C, 55.68; H, 7.62; N, 6.83

Found: C, 55.53; H, 7.30; N, 6.59

Example 27

1-[2-(4-Methyl-1-piperazinyl)-1-[3-(trifluoromethyl)phenyl]-ethyl]cyclohexanol

By replacing 1-(3-methoxyphenyl)acetyl-4-phenylmethylpiperazine in Example 15 with a molar equivalent amount of 4-methyl-1-[(3-trifluoromethylphenyl)acetyl]piperazine, the title compound was obtained as the dihydrochloride, m.p. 245-248°C.

Elemental Analysis for: $C_{20}H_{29}N_2OF_3 \cdot 2\ HCl$

Calculated: C, 54.17; H, 7.04; N, 6.32

Found: C, 53.74; H, 6.86; N, 6.56

Example 28

1-[1-(4-Methoxyphenyl)-2-(4-methyl-1-piperazinyl)-ethyl]cyclohexanol

By replacing 1-(3-methoxyphenyl)acetyl-4-phenylmethylpiperazine in Example 15 with a molar equivalent amount of 1-(4-methoxyphenyl)acetyl-4-methylpiperazine, the title compound was obtained as a dihydrochloride, m.p. 234-236°C.

Elemental Analysis for:	$C_{20}H_{32}N_2O_2 \cdot 2HCl$
Calculated:	C, 59.53; H, 8.57; N, 6.95
Found:	C, 59.56; H, 8.27; N, 6.69

Example 29

1-[1-(3-Bromo-4-methoxyphenyl)-2-[4-(phenylmethyl)-1-piperazinyl]-ethyl]cyclohexanol

The title compound is obtained by first replacing 3-methoxyphenyl acetic acid in IV(a) with a molar equivalent amount of 3-bromo-4-methoxyphenyl acetic acid and using the amide obtained therein as a replacement for 1-(3-methoxyphenyl)acetyl-4-(phenylmethyl)piperazine in Example 15.

Example 30

1-[1-(4-Methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]butyl]cyclohexanol

Following the procedure of Example 22, the intermediate produced in paragraph III(b), supra, is hydrogenated to obtain 1-[1-(4-methoxyphenyl)-4-(1-piperazinyl)butyl]cyclohexanol, which is rebenzylated routinely following the procedure indicated in the same example to give the title compound.

The antidepressant activity of the compounds of this invention was established by demonstrating their ability to inhibit synaptosomal uptake of norepinephrine (^{3}H-NE) and/or serotonin (^{14}C-5-HT) following the test procedure of Wood et al., J. Neurochem., 37 795 (1981). The pharmacology of the compounds of Examples 26 and 27 typifies selective antidepressant activity.

The additional anxiolytic property possessed by some of the compounds of this invention was indicated by demonstrating their strong affinity at 5-HT_{1A} receptor binding sites through inhibition of [^{3}H] 8-hydroxy-2-(di-n-propylamino)tetralin binding at 5-HT binding sites in rat hippocampal tissue, following the procedure of Hall et al., J. Neurochem., 44 1685 (1985). Typical of these compounds are the products of Examples 1 and 5.

Furthermore, as may be seen from the pharmacological data presented infra, some of the compounds embraced by the compound genus of this invention demonstrate relatively high affinity for dopamine D_2 receptors, which is indicative of antipsychotic activity [Seeman, Pharmacol. Rev. 32, 230 (1981)]. Examples of these compounds are those demonstrating in excess of about 60% inhibition of ^{3}H-haloperidol binding at D_2 receptors found in homogenized limbic brain tissue at 1μM concentration of the test compound as determined in a modification of the test procedure of Fields et al., Brain Res., 136, 578 (1977) and Yamamura et al., eds., Neurotransmitter Receptor Binding, Raven Press, N.Y. (1978) as discussed in U.S. 4,636,563. The actual percentage reduction of ^{3}H-haloperidol binding is reported infra and the larger the number, the greater the potential for dopamine D_2 receptor binding and antipsychotic activity. The products of Examples 4 and 11 demonstrate typical D_2 binding potential for those compounds with that property aspect of a generally recognized antipsychotic profile.

The pharmacological test data obtained for a representative number of compounds of this invention in accordance with the standard experimental test procedures disclosed above appear in the following table:

	Receptor Binding Ki(nM) or % Inhibition at 1μM		Neuronal Uptake IC_{50}(μM) or % Inhibition at 10μM	
Compound	$5HT_{1A}$	D_2	NE	5HT
Example 1	10 nM	209 nM	2.03 μM	0.39 μM
Example 2	78%	59%		
Example 3	122 nM	41%		
Example 4	66%	90%		
Example 5	97%	51%	100%	100%
Example 6	93%	91%		
Example 7	93%	89%		
Example 8	99%	55%	0.61 μM	67%
Example 9	57%	15%		
Example 10	99%	73%		
Example 11	100%	100%		
Example 12	100%	95%		
Example 13	93%	77%		
Example 14	63%	25%		
Example 15	91%	90%		
Example 18	97%	39%	38%	62%
Example 19	94%	32%		
Example 24		11%		
Example 26	0	26%	0.18 μM	33%
Example 27	5%	0%	86%	0
Buspirone	10 nM (97%)	84% (78 nM)		

In qualitatively evaluating the above data, high activity values in NE and 5-HT uptake correlate with antidepressant activity; high activity values for inhibition of 5-HT_{1A} binding (about 90% to 100%) correlate (by analogy with buspirone) with anxiolytic activity; high affinity values for D_2 receptor binding (greater than 80%) correlate with antipsychotic activity.

From these data, the activity profile of the compounds of this invention are seen to be useful in the treatment of psychiatric disorders, in some instances, combining very desirable antidepressant-anxiolytic properties or demonstrating pure antidepressant activity.

Hence, the compounds of this invention are antidepressant, antipsychotic and anxiolytic agents useful in the treatment of depression and in alleviating anxiety. As such, they may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both of pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers

for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oil ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellent.

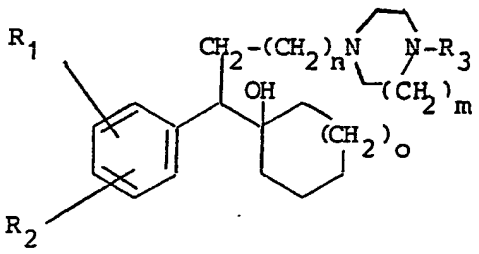
Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or table itself, or it can be the appropriate number of any such compositions in package form.

The dosage to be used in the treatment of a specific psychiatric disorder must be subjectively determined by the attending physician. The variables involved include the specific psychosis or state of depression or anxiety and the size, age and response pattern of the patient.

CLAIMS

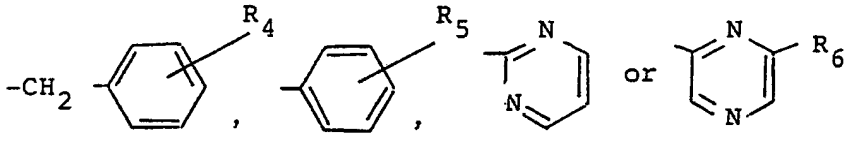
1. A compound of the formula:



(I)

in which

m is one of the integers 1,2 or 3;
n is one of the integers 0,1 or 2;
o is one of the integers 0,1 or 2;
R_1 and R_2 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, trifluoromethyl, halo, or, when taken together, 3,4-methylenedioxy;
R_3 is alkyl of 1 to 3 carbon atoms,

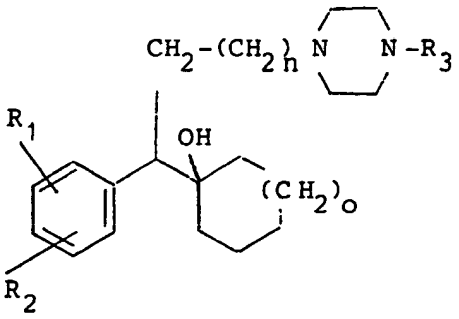


;

where R_4 and R_5 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, halo or trifluoromethyl; and

R_6 is hydrogen or halo;
or a pharmaceutically acceptable salt thereof.

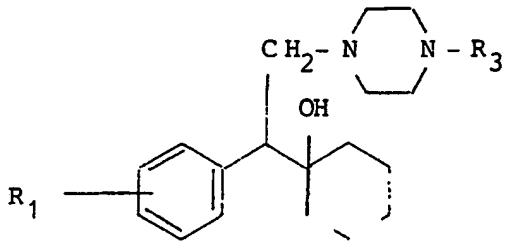
2. A compound as claimed in Claim 1 of the formula:



in which

n is one of the integers 0,1 or 2;
o is one of the integers 0,1 or 2;
R_1 is hydrogen, alkoxy of 1 to 3 carbon atoms or hydroxy;
R_2 is alkoxy of 1 to 3 carbon atoms or hydroxy and, when R_1 is hydrogen and n is zero, R_2 can be halo or trifluoromethyl;
or R_1 and R_2 taken together are 3,4-methylenedioxy; and
R_3 is benzyl, chlorobenzyl, trifluoromethylbenzyl, alkoxybenzyl, chlorophenyl, trifluoromethylphenyl or alkoxyphenyl in which said alkoxy groups contain 1 to 3 carbon atoms; or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 of the formula:



in which

R_1 is halo, trifluoromethyl, hydroxy or alkoxy of 1 to 6 carbon atoms;and R_3 is alkyl of 1 to 3 carbon atoms or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 1 which is

1-[1-(3-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]propyl]cyclohexanol, or

1-[1-(3-methoxyphenyl)-3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]cyclohexanol, or

1-[3-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)propyl]cyclohexanol, or

1-[3-[4-[(4-chlorophenyl)methyl]methyl]-1-piperazinyl]-1-(3-methoxyphenyl)propyl]cyclohexanol or

1-[1-(3-methoxyphenyl)-3-[4-[(2-methoxyphenylmethyl]-1-piperazinyl]propyl]cyclohexanol, or

1-[3-[4-[(3-fluorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)propyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-3-[4-(phenylmethyl)-1-piperazinyl]propyl]cyclohexanol, or

1-[3-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]-1-(4-methoxyphenyl)propyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-3-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]propyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-3-[4-[[3-(trifluoromethyl)-phenyl]methyl]-1-piperazinyl]propyl]cyclohexanol, or

1-[3-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-(4-methoxyphenyl)propyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-3-[4-(2-methoxyphenyl)methyl]-1-piperazinyl]propyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-3-[4-[[4-(trifluoromethyl)-phenyl]-methyl]-1-piperazinyl]propyl]-cyclohexanol, or

1-[1-(3-methoxyphenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol, or

1-[2-[4-(phenylmethyl)-1-piperazinyl]-1-[3-(trifluoro-methyl)phenyl]ethyl]cyclohexanol, or

1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol, or

1-[2-[4-(3-chlorophenyl)-1-piperazinyl]-1-(3-methoxy-phenyl)ethyl]cyclohexanol, or

1-[1-(3-chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol, or

1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]cyclo-hexanol, or

1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclopentanol, or

1-[2-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-(3-methoxyphenyl)ethyl]cyclohexanol, or

1-[2-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]-1-(3-methoxyphenyl)ethyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]cyclohexanol, or

1-[1-(3-fluorophenyl)-2-(4-methyl)-1-piperazinyl-ethyl]cyclohexanol, or

1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol, or

1-[2-(4-methyl-1-piperazinyl)-1-[3-(trifluoromethyl)phenyl]ethyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-2-(4-methyl-1-piperazinyl)-ethyl]cyclohexanol, or

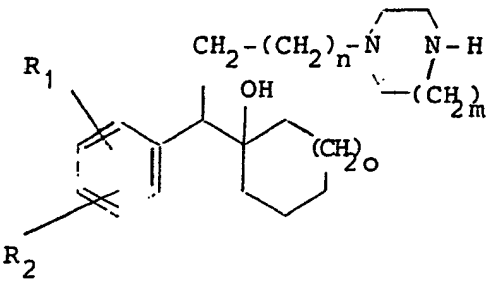
1-[1-(3-bromo-4-methoxyphenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol, or

1-[1-(4-methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]butyl]cyclohexanol,

or a pharmaceutically acceptable salt thereof.

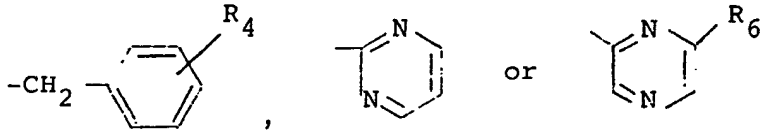
5. A process for preparing a compound claimed in claim 1 which comprises

(a) alkylating a compound of a formula



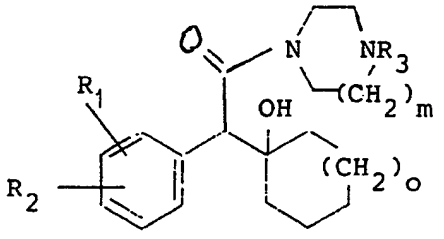
(II)

where m,n,o,R_1 and R_2 have the meanings given in claim 1, with an alkylating agent containing the R_3. radical (where R_3. is



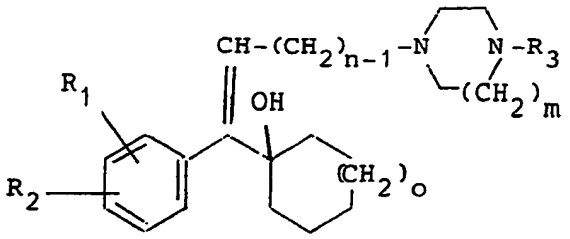
where R_4 and R_6 have the meanings given in claim 1) or

(b) reducing a compound of formula



(III)

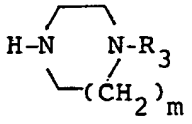
or



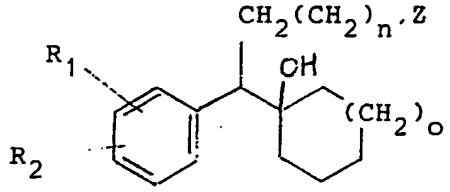
(IV)

(where m,n,o,R_1,R_2 and R_3 have the meanings given in claim 1) or

(c) reacting a heterocyclic compound of formula



(where m and R_3 have the meanings given in claim 1) with a compound of formula



(V)

(where o, R1 and R2 have the meanings given in claim 1, n' is 1 or 2 and Z is a leaving group) or

(d) reacting a free base of formula (I) with an acid to form a pharmaceutically acceptable salt of the compound of formula I or

(e) resolving a racemic mixture of the compound of formula I or a pharmaceutically acceptable salt thereof.

6. A process as claimed in claim 5 which comprises alkylating a compound of formula (II) with a compound of formula $R_3.X$ (where R_3 is as defined in claim 5 and X is a leaving group).

7. A process as claimed in claim 5 which comprises reducing a compound of formula (III) with a hydride reducing agent.

8. A process as claimed in claim 5 which comprises reducing a compound of formula (IV) by catalytic hydrogenation and, if necessary, alkylating the product to introduce the desired R_3 group.

9. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 and a pharmaceutically acceptable carrier therefore.

10. A compound as claimed in any one of claims 1 to 4 for use as a pharmaceutical.

11. A compound as claimed in claim 2 for use as an antidepressant/anxiolytic.

12. A compound as claimed in claim 3 for use as an antidepressant.

13. A process for preparing a compound claimed in Claim 1 substantially as hereinbefore described with reference to any one of the Examples.

14. A compound as claimed in Claim 1 whenever prepared by the process claimed in any one of Claims 5 to 8 and 13.

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